

AD_____

Award Number: MIPR0JDAVM0112

TITLE: Effects of Repeated Traumatic Brain Injuries in a Combat Setting

PRINCIPAL INVESTIGATOR: Andrew J. MacGregor, Ph.D.

CONTRACTING ORGANIZATION: Naval Health Research Center
San Diego, CA 92106-3521

REPORT DATE: December 2011

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.					
1. REPORT DATE December 2011		2. REPORT TYPE Final		3. DATES COVERED 1 June 2010 – 30 November 2011	
4. TITLE AND SUBTITLE Effects of Repeated Traumatic Brain Injuries in a Combat Setting				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER MIPR0JDAVM0112	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Andrew J. MacGregor E-Mail: Andrew.MacGregor@med.navy.mil				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Naval Health Research Center San Diego, CA 92106-3521				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT Traumatic brain injury (TBI) is considered one of the signature wounds of the current conflicts in Iraq and Afghanistan. Compared to previous wars and because of advancements in battlefield medical care and personal protective equipment, many casualties survive these wounds and are returned to duty. However, those service members who return to duty following mild TBI, or concussion, are at risk for repeated injury. The effects of repeated TBI among U.S. service members have not been examined. This study for the first time described the occurrence of repeated TBI among military deployed personnel, and identified time between repeated TBI events. The median time between repeated TBI events was 40 days. Severity of the 2nd event, but not 1st event, was predictive of adverse neurological and psychological outcomes. Results of the aforementioned analysis have been published in the Journal of Rehabilitation Research and Development (MacGregor, 2011). An analysis is currently underway that is examining repeated TBI events compared with single TBI events and an injured, non-TBI control group. The results of this study may have a direct impact on military policy, as guidelines are currently being considered to address the management of combat-related TBI.					
15. SUBJECT TERMS TBI, repeated, neurological, psychological, military, combat					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	9	19b. TELEPHONE NUMBER (include area code)

Table of Contents

	<u>Page</u>
Introduction.....	4
Body.....	4
Key Research Accomplishments.....	5
Reportable Outcomes.....	6
Conclusion.....	6
References.....	6
Appendix.....	9

INTRODUCTION

Traumatic brain injury (TBI), or concussion, is considered one of the signature wounds of the current conflicts in Iraq and Afghanistan. Compared to previous wars and because of advancements in battlefield medical care and personal protective equipment, many casualties survive these wounds and are returned to duty. However, those service members who return to duty following mild TBI are at risk for repeated injury. In civilians, especially athletes, repeated TBI is associated with adverse outcomes, such as dementia. The effects of repeated TBI among U.S. service members have not been examined. This study examined repeated TBI using medical records collected near the point of injury in Iraq, which also allowed for calculation of time between TBI events. The results of this study may have a direct impact on military policy, as guidelines are currently being considered to address the management of combat-related TBI. For the purposes of the remainder of this report, TBI will be used interchangeably with concussion.

BODY (Please refer to the Appendix: MacGregor, 2011, to find the published article that is referred to below)

Specific Aim #1: Define the demographic and injury specific characteristics of repeated traumatic brain injury (TBI) during Operation Iraqi Freedom (OIF).

Task 1. Data extraction from multiple existing data sources to assemble the repeated TBI cohort and define individual personnel characteristics. (months 1-2)

1a. Identify personnel from the Tri-Service Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database (Navy-Marine Corps CTR EMED) with more than one clinically diagnosed TBI during OIF. (month 1)

1b. Link injured personnel with Defense Manpower Data Center and DEERS information for demographic and deployment-specific variables. (month 2)

Update: This task has been completed. The final study population consisted of 113 individuals with repeated TBI. The results were published recently (MacGregor, 2011).

Task 2. Identify correlates of increased severity of second TBI event. (month 3)

2a. Identify severity of each individual TBI event. (month 3)

2b. Calculate time between TBI events for all personnel with repeated TBI. (month 3)

2c. Identify disposition (i.e. returned to duty, light duty, evacuated, etc.) for all personnel with repeated TBI. (month 3)

Update: This task has been completed, and the results were recently published (MacGregor, 2011).

Severity of 2nd event was a predictor of mental and neurological outcomes, but severity of 1st event was not associated. Severity of 1st event was not associated with severity of 2nd event.

Task 3. Assess occupational risk of repeated TBI. (month 4)

3a. Select representative sample of single TBI events from Navy-Marine Corps CTR EMED. (month 4)

3b. Compare Military Occupational Specialties utilizing chi-square statistics. (month 4)

Update: Analysis for this task is currently underway. The cohort of single and repeated TBI events has been identified, and the analysis has begun.

Task 4. Prepare manuscript for publication encompassing specific aim #1. (months 5-6)

4a. Complete manuscript draft. (month 5)

4b. Edit and format per journal requirements. (months 5-6)

4c. Submit for release authority through public affairs office. (month 6)

Update: This task has been completed with the exception of task 4 (MacGregor, 2011). The results of this task will be published in the 2nd manuscript on specific aim 2.

Specific Aim #2: Identify health care utilization, mental health outcomes and attrition rates among those with repeated TBI and compare with multiple injured control groups.

Task 1. Data extraction from multiple existing data sources to assemble the injured control groups. (months 7-8)

1a. Identify control group A from the Navy-Marine CTR EMED; personnel with one non-TBI event and a subsequent TBI event. (month 7)

1b. Identify control group B from the Navy-Marine CTR EMED; personnel with two non-TBI events. (month 7)

1c. Link injured personnel with Defense Manpower Data Center and DEERS information for demographic and deployment-specific variables. (month 8)

Update: This task has been completed. The single and repeated TBI cohort has been identified. Additionally, an injured control group of non-head injuries has also been identified. Data analysis has begun.

Task 2. Identify post-injury medical utilization using Military Health System records. (months 9-12)

2a. Identify specific number of general inpatient and outpatient health care visits for the study population. (months 9-10)

2b. Identify specific number of mental health inpatient and outpatient health care visits for the study population. (months 10-11)

2c. Identify specific inpatient and outpatient mental health diagnoses for the study population and group into categories (i.e. anxiety, mood, adjustment, and substance abuse disorders). (months 11-12)

Update: This task is currently underway, data analysis has begun on the study population.

Task 3. Utilize regression modeling to assess relationship between repeated TBI and subsequent health outcomes. (months 12-14)

3a. Utilize regression techniques for analysis of general and mental health care visits. (months 12-13)

3b. Utilize regression techniques for analysis of mental health diagnoses. (month 13)

3c. Utilize regression techniques for analysis of military attrition. (month 14)

3d. Repeat regression analyses following adjustment for potential confounding demographic and injury specific variables. (months 13-14)

Update: This task is currently underway, data analysis has begun on the study population.

Specific Aim #3: Examine the potential protective effect of time between TBI events.

Task 1. Repeat regression analyses outlined in specific aim #2, task 3. (months 15-16)

1a. Utilize the time between TBI events as both a continuous and categorical variable. (months 15-16)

1b. Assess any interaction with disposition following TBI events. (months 15-16)

Update: This task has not yet been initiated, as data analysis for previous tasks is still underway. However, time was examined for its potential protective effect on severity of 2nd event. There was no association, and this is included in the manuscript that was recently published (MacGregor, 2011).

Task 2. Prepare manuscript for publication encompassing specific aims #1 and #2. (months 16-18)

2a. Complete manuscript draft. (months 16-17)

2b. Edit and format per journal requirements. (months 17-18)

2c. Submit for release authority through public affairs office. (month 18)

Update: This task has not yet been initiated, as data analysis is still underway. However the literature review has been continually updated, and many of the methods for the first published manuscript carry over to this one (MacGregor, 2011).

KEY RESEARCH ACCOMPLISHMENTS

- First study to examine repeated TBI in deployed military personnel
- Added to the literature on the effects of time between repeated TBI events, a subject sparsely researched even in the civilian community
- Identified future areas of research to further knowledge on repeated TBI

REPORTABLE OUTCOMES

MacGregor AJ, Dougherty AL, Morrison RA, Quinn KH, Galarneau MR. Repeated concussion among U.S. military personnel during Operation Iraqi Freedom. In Press, Journal of Rehabilitation Research and Development.

MacGregor AJ, Morrison RH, Dougherty AL, Galarneau MR, Mayo JM. Repeated traumatic brain injury: Are military personnel a high risk occupational group? Poster presented at the Forty-Ninth Navy and Marine Corps Public Health Conference, Hampton, Virginia, March 2010.

CONCLUSIONS

More research is needed to examine the cumulative effects, if any, of repeated concussion among military personnel. The first published article from this research (MacGregor, 2011) is the initial investigation of the topic and is mostly descriptive in nature. No effect of severity of the 1st TBI event was found. This may have been due to small sample size, however. Severity of the 2nd TBI event was predictive of adverse psychological and neurological outcome. The median time between TBI events was 40 days, but time was not associated with poor outcome. The analysis that is currently underway will add to the body of literature by bringing in single TBI events and non-head injuries as comparison groups. Future studies should prospectively examine repeated TBI in a large cohort of military personnel in order to maximize sample size. The final results of the present analysis will advance discussion on future military TBI policies, to include restriction from duty following a certain number of TBI events.

REFERENCES

- Barth, J. T., Alves, W. M., Ryan, T. V., Macciocchi, S. N., Rimel, R. W., Jane, J. A., et al. (1987). Mild head injury in sports: neuropsychological sequelae and recovery of function. In H. s. Levin (Ed.), *Mild head injury* (pp. 257-275). New York: Oxford University Press.
- Belanger, H. G., Spiegel, E., & Vanderploeg, R. D. (2010). Neuropsychological performance following a history of multiple self-reported concussions: a meta-analysis. *J Int Neuropsychol Soc*, 16(2), 262-267.
- Bruce, J. M., & Echemendia, R. J. (2009). History of multiple self-reported concussions is not associated with reduced cognitive abilities. *Neurosurgery*, 64(1), 100-106; discussion 106.
- Cantu, R. C. (1998). Second-impact syndrome. *Clin Sports Med*, 17(1), 37-44.
- Cantu, R. C. (2003). Recurrent athletic head injury: risks and when to retire. *Clin Sports Med*, 22(3), 593-603, x.
- Cernak, I., & Noble-Haeusslein, L. J. (2010). Traumatic brain injury: an overview of pathobiology with emphasis on military populations. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.Review]. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism*, 30(2), 255-266.
- Cernak, I., Savic, J., Malicevic, Z., Zunic, G., Radošević, P., Ivanovic, I., et al. (1996). Involvement of the central nervous system in the general response to pulmonary blast injury. *The Journal of trauma*, 40(3 Suppl), S100-104.
- Cernak, I., Wang, Z., Jiang, J., Bian, X., & Savic, J. (2001). Ultrastructural and functional characteristics of blast injury-induced neurotrauma. *The Journal of trauma*, 50(4), 695-706.
- Chavko, M., Watanabe, T., Adeeb, S., Lankasky, J., Ahlers, S. T., & McCarron, R. M. (2011). Relationship between orientation to a blast and pressure wave propagation inside the rat brain. [Research Support, U.S. Gov't, Non-P.H.S.]. *Journal of neuroscience methods*, 195(1), 61-66.

- Collie, A., McCrory, P., & Makdissi, M. (2006). Does history of concussion affect current cognitive status? *Br J Sports Med*, 40(6), 550-551.
- Collins, M. W., Grindel, S. H., Lovell, M. R., Dede, D. E., Moser, D. J., Phalin, B. R., et al. (1999). Relationship between concussion and neuropsychological performance in college football players. *JAMA*, 282(10), 964-970.
- Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery*, 51(5), 1175-1179; discussion 1180-1171.
- Covassin, T., Elbin, R., Kontos, A., & Larson, E. (2010). Investigating baseline neurocognitive performance between male and female athletes with a history of multiple concussion. *J Neurol Neurosurg Psychiatry*, 81(6), 597-601.
- Covassin, T., Stearne, D., & Elbin, R. (2008). Concussion history and postconcussion neurocognitive performance and symptoms in collegiate athletes. *J Athl Train*, 43(2), 119-124.
- Creeley, C. E., Wozniak, D. F., Bayly, P. V., Olney, J. W., & Lewis, L. M. (2004). Multiple episodes of mild traumatic brain injury result in impaired cognitive performance in mice. *Acad Emerg Med*, 11(8), 809-819.
- De Beaumont, L., Brisson, B., Lassonde, M., & Jolicoeur, P. (2007). Long-term electrophysiological changes in athletes with a history of multiple concussions. *Brain Inj*, 21(6), 631-644.
- DeRoss, A. L., Adams, J. E., Vane, D. W., Russell, S. J., Terella, A. M., & Wald, S. L. (2002). Multiple head injuries in rats: effects on behavior. *J Trauma*, 52(4), 708-714.
- Friess, S. H., Ichord, R. N., Ralston, J., Ryall, K., Helfaer, M. A., Smith, C., et al. (2009). Repeated traumatic brain injury affects composite cognitive function in piglets. *J Neurotrauma*, 26(7), 1111-1121.
- Gaetz, M., Goodman, D., & Weinberg, H. (2000). Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj*, 14(12), 1077-1088.
- Graves, A. B., White, E., Koepsell, T. D., Reifler, B. V., van Belle, G., Larson, E. B., et al. (1990). The association between head trauma and Alzheimer's disease. *Am J Epidemiol*, 131(3), 491-501.
- Gronwall, D., & Wrightson, P. (1975). Cumulative effect of concussion. *Lancet*, 2(7943), 995-997.
- Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Cantu, R. C., Randolph, C., et al. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, 57(4), 719-726; discussion 719-726.
- Guskiewicz, K. M., Marshall, S. W., Bailes, J., McCrea, M., Harding, H. P., Jr., Matthews, A., et al. (2007). Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*, 39(6), 903-909.
- Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., et al. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA*, 290(19), 2549-2555.
- Iverson, G. (2007). Predicting slow recovery from sport-related concussion: the new simple-complex distinction. *Clin J Sport Med*, 17(1), 31-37.
- Iverson, G. L., Brooks, B. L., Lovell, M. R., & Collins, M. W. (2006). No cumulative effects for one or two previous concussions. *Br J Sports Med*, 40(1), 72-75.
- Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Inj*, 18(5), 433-443.
- Jordan, B. D. (2000). Chronic traumatic brain injury associated with boxing. *Semin Neurol*, 20(2), 179-185.
- Long, J. B., Bentley, T. L., Wessner, K. A., Cerone, C., Sweeney, S., & Bauman, R. A. (2009). Blast overpressure in rats: recreating a battlefield injury in the laboratory. *Journal of neurotrauma*, 26(6), 827-840.
- Mac Donald, C. L., Johnson, A. M., Cooper, D., Nelson, E. C., Werner, N. J., Shimony, J. S., et al. (2011). Detection of blast-related traumatic brain injury in U.S. military personnel. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, Non-P.H.S.]. *The New England journal of medicine*, 364(22), 2091-2100.
- Macciocchi, S. N., Barth, J. T., Littlefield, L., & Cantu, R. C. (2001). Multiple Concussions and Neuropsychological Functioning in Collegiate Football Players. *J Athl Train*, 36(3), 303-306.
- Matser, E. J., Kessels, A. G., Lezak, M. D., Jordan, B. D., & Troost, J. (1999). Neuropsychological impairment in amateur soccer players. *JAMA*, 282(10), 971-973.

- Matser, J. T., Kessels, A. G., Jordan, B. D., Lezak, M. D., & Troost, J. (1998). Chronic traumatic brain injury in professional soccer players. *Neurology*, 51(3), 791-796.
- Matser, J. T., Kessels, A. G., Lezak, M. D., & Troost, J. (2001). A dose-response relation of headers and concussions with cognitive impairment in professional soccer players. *J Clin Exp Neuropsychol*, 23(6), 770-774.
- Mortimer, J. A., French, L. R., Hutton, J. T., & Schuman, L. M. (1985). Head injury as a risk factor for Alzheimer's disease. *Neurology*, 35(2), 264-267.
- Moser, R. S., & Schatz, P. (2002). Enduring effects of concussion in youth athletes. *Arch Clin Neuropsychol*, 17(1), 91-100.
- Pellman, E. J., Viano, D. C., Casson, I. R., Tucker, A. M., Waeckerle, J. F., Powell, J. W., et al. (2004). Concussion in professional football: repeat injuries--part 4. *Neurosurgery*, 55(4), 860-873; discussion 873-866.
- Perez-Pinzon, M. A., Alonso, O., Kraydieh, S., & Dietrich, W. D. (1999). Induction of tolerance against traumatic brain injury by ischemic preconditioning. *Neuroreport*, 10(14), 2951-2954.
- Readnower, R. D., Chavko, M., Adeeb, S., Conroy, M. D., Pauly, J. R., McCarron, R. M., et al. (2010). Increase in blood-brain barrier permeability, oxidative stress, and activated microglia in a rat model of blast-induced traumatic brain injury. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Journal of neuroscience research*, 88(16), 3530-3539.
- Saunders, L. L., Selassie, A. W., Hill, E. G., Nicholas, J. S., Horner, M. D., Corrigan, J. D., et al. (2009). A population-based study of repetitive traumatic brain injury among persons with traumatic brain injury. *Brain Inj*, 23(11), 866-872.
- Schaller, B., & Graf, R. (2002). Cerebral ischemic preconditioning. An experimental phenomenon or a clinical important entity of stroke prevention? *J Neurol*, 249(11), 1503-1511.
- Scheibel, R. S., Newsome, M. R., Troyanskaya, M., Lin, X., Steinberg, J. L., Radaideh, M., et al. (2011). Altered Brain Activation in Military Personnel with One or More Traumatic Brain Injuries Following Blast. *Journal of the International Neuropsychological Society : JINS*, 1-12.
- Schmidt, M. L., Zhukareva, V., Newell, K. L., Lee, V. M., & Trojanowski, J. Q. (2001). Tau isoform profile and phosphorylation state in dementia pugilistica recapitulate Alzheimer's disease. *Acta Neuropathol*, 101(5), 518-524.
- Slobounov, S., Cao, C., & Sebastianelli, W. (2009). Differential effect of first versus second concussive episodes on wavelet information quality of EEG. *Clin Neurophysiol*, 120(5), 862-867.
- Slobounov, S., Slobounov, E., Sebastianelli, W., Cao, C., & Newell, K. (2007). Differential rate of recovery in athletes after first and second concussion episodes. *Neurosurgery*, 61(2), 338-344; discussion 344.
- Sports-related recurrent brain injuries--United States. (1997). *MMWR Morb Mortal Wkly Rep*, 46(10), 224-227.
- Taber, K. H., Warden, D. L., & Hurley, R. A. (2006). Blast-related traumatic brain injury: what is known? *The Journal of neuropsychiatry and clinical neurosciences*, 18(2), 141-145.
- Tanriverdi, F., Unluhizarci, K., & Kelestimur, F. (2010). Pituitary function in subjects with mild traumatic brain injury: a review of literature and proposal of a screening strategy. *Pituitary*, 13(2), 146-153.
- Teasdale, T. W., & Engberg, A. W. (2003). Cognitive dysfunction in young men following head injury in childhood and adolescence: a population study. *J Neurol Neurosurg Psychiatry*, 74(7), 933-936.
- Theriault, M., De Beaumont, L., Gosselin, N., Filipinni, M., & Lassonde, M. (2009). Electrophysiological abnormalities in well functioning multiple concussed athletes. *Brain Inj*, 23(11), 899-906.
- Theriault, M., De Beaumont, L., Tremblay, S., Lassonde, M., & Jolicoeur, P. (2011). Cumulative effects of concussions in athletes revealed by electrophysiological abnormalities on visual working memory. *J Clin Exp Neuropsychol*, 33(1), 30-41.
- Thornton, A. E., Cox, D. N., Whitfield, K., & Fouladi, R. T. (2008). Cumulative concussion exposure in rugby players: neurocognitive and symptomatic outcomes. *J Clin Exp Neuropsychol*, 30(4), 398-409.
- Wall, S. E., Williams, W. H., Cartwright-Hatton, S., Kelly, T. P., Murray, J., Murray, M., et al. (2006). Neuropsychological dysfunction following repeat concussions in jockeys. *J Neurol Neurosurg Psychiatry*, 77(4), 518-520.
- Wang, Y., Wei, Y., Oguntayo, S., Wilkins, W., Arun, P., Valiyaveetil, M., et al. (2011). Tightly coupled repetitive blast-induced traumatic brain injury: development and characterization in mice. *Journal of neurotrauma*, 28(10), 2171-2183.

Weber, J. T. (2007). Experimental models of repetitive brain injuries. *Prog Brain Res*, 161, 253-261.

APPENDIX

MacGregor AJ, Dougherty AL, Morrison RH, Quinn KH, Galarneau MR. Repeated concussion among U.S. military personnel during Operation Iraqi Freedom. *J Rehabil Res Dev*. 2011;48(10):1269-78. Available at:
<http://www.rehab.research.va.gov/jour/11/4810/pdf/macgregor4810.pdf>